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Research Article

FORMULATION AND EVALUATION OF ETORICOXIB SOLID DISPERSIONS EMPLOYING STARCH PHOSPHATE, PVP AND PEG 4000 – A FACTORIAL STUDY

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ABSTRACT

Solid dispersion is a widely accepted technique for enhancing the dissolution rate of poorly soluble BCS class II drugs. The objective of the present study is to evaluate starch phosphate- a new modified starch, PVP K-30 and PEG 4000 as carriers in solid dispersions for enhancing the dissolution rate and efficiency of etoricoxib, a BCS class II drug. The individual main and combined effects of the three factors namely starch phosphate (factor A), PVP K- 30 (factor B) and PEG 4000 (factor C) in enhancing the dissolution rate and dissolution efficiency of etoricoxib were evaluated in a 2^3- factorial study. Starch phosphate (F_a) gave highest enhancement in the dissolution rate of etoricoxib (26.7 fold) followed by PEG 4000 (F_c) (10.54 fold) and PVP (F_b) (8.04 fold). DE_{30} was also increased from 3.03% for etoricoxib pure drug (F_1) to 55.28, 46.36 and 36.61 % respectively with solid dispersions F_a, F_c and F_b. Addition of PVP and PEG 4000 to the solid dispersions in starch phosphate has further increased the dissolution rate upto 200.59 fold and dissolution efficiency upto 29.15 fold. Hence addition of PVP and PEG 4000 to the solid dispersions in starch phosphate is recommended to enhance the dissolution rate of etoricoxib, a BCS class II drug.

Key words: Solid dispersions, Etoricoxib, Starch Phosphate, PVP K-30, PEG 4000, Factorial Study.

INTRODUCTION

Etoricoxib, a widely prescribed anti inflammatory and analgesic drug belong to Class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. Several techniques[1] such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility , microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among the various approaches, solid dispersions in water dispersible excipients is a simple, industrially useful approach for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs.

Starch phosphate is one of the modified starches used in the frozen food industry [2, 3]. It is produced by phosphorification of free hydroxyl groups of anhydroglucose units of starch molecule. We have earlier reported the preparation characterization and evaluation of starch phosphate as an efficient disintegrant in tablet formulations [4].

The objective of the present study is to evaluate starch phosphate (a new modified starch), PVP and PEG 4000 as a carriers in solid dispersions for enhancing the dissolution rate of etoricoxib. Their individual and combined (interaction) effects in enhancing the dissolution rate and dissolution efficiency of etoricoxib were evaluated in a 2^3- factorial study.

MATERIALS AND METHODS

Materials

Etoricoxib was gift sample from M/s Dr. Reddys Laboratory, Hyderabad, starch phosphate was prepared in the laboratory, Dichloromethane (Qualigens), potato starch (S.D Fine Chemicals), Methanol (S.D Fine Chemicals), were procured from commercial sources.

Methods

Preparation of Starch Phosphate

Starch phosphate was prepared based on the method of Choi *et al*[5] with some modifications. Potato starch (100 g) and di-sodium hydrogen orthophosphate anhydrous (30 g) were suspended in 100 ml of water and continuously stirred for 20 min. This starch slurry was then filtered and the wet starch mixture was conditioned for 12 h at room temperature (28^0C). To enhance phosphorylation, this mixture was heated in a forced air oven at 130 °C for 3 h. The product obtained was ground and sized.

Estimation of Etoricoxib

An UV spectrophotometric method based on the measurement of absorbance at 288 nm in phosphate buffer pH 7.4 was used for estimation of etoricoxib. The method obeyed Beer- Lambert's law in the concentration range of 1-10 µm/mL. When the standard drug solution was assayed repeatedly (n=6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.60% and 1.0% respectively. No interference from excipients used was observed.

Formulation of Etoricoxib Solid Dispersions as per 2^3 Factorial Study

In the 2^3 factorial study, the three factors namely starch phosphate (factor A), PVP K -30 (factor B) and PEG 4000 (factor C) each at two levels were investigated for their individual and combined effects on the dissolution rate of etoricoxib solid dispersions. Starch phosphate (factor A) was used as a carrier at a drug: carrier ratio of 1:2 and hence the two levels of starch phosphate (factor A) were 0 and 1:2 ratio of drug: carrier. PVP K -30 (factor B) and PEG 4000 (factor C) and were studied each at two levels i.e. 0% and 2% concentration.. A total of eight etoricoxib solid dispersions were prepared employing selected combinations of the three factors.

Preparation of Solid Dispersions of Etoricoxib in Starch Phosphate

Solid dispersions of etoricoxib in starch phosphate were prepared employing selected combinations of the three factors by solvent evaporation method. Etoricoxib was dissolved in dichloromethane (10 ml) in a dry mortar to get a clear solution. Starch phosphate/PVP/PEG 4000 were then added and mixed. The thick slurry was triturated for 15 min for complete evaporation of dichloromethane and then dried at 55^oC until dry. The dried mass was pulverized and sieved through mesh no. 100.

Dissolution Rate Study

Dissolution rate of etoricoxib as such and from its solid dispersions prepared was studied in phosphate buffer pH 7.4 (900 ml) employing USP 8 station Dissolution Rate Test Apparatus (M/s

Labindia Disso 8000) with a paddle stirrer at 50 rpm. Etoricoxib or its solid dispersions equivalent of 60 mg of etoricoxib was used in each test. A temperature 37±1°C was maintained in each test. Samples of dissolution medium (5 ml) were withdrawn through a filter (0.45µ) at different time intervals and assayed for etoricoxib at 288nm. All the dissolution experiments were replicated four times each (n=4).

RESULTS AND DISCUSSION

To evaluate the individual main and combined effects of starch phosphate (factor A), PVP K-30 (factor B) and PEG 4000 (factor C) on the dissolution rate of etoricoxib, solid dispersions of etoricoxib were prepared employing selected combinations of the three factors as per 2^3 - factorial study. All the solid dispersions prepared were fine and free flowing powders. Drug content was uniform in each batch of solid dispersion prepared (c.v < 2%).

The dissolution of etoricoxib from all the solid dispersions prepared was studied in phosphate buffer pH 7.4 (n=4). The dissolution profiles of various solid dispersions prepared are shown in Fig.1. Dissolution data were analyzed as per zero order and first order kinetic models. The correlation coefficient 'r' values in the first order model were higher than those in the zero order model in all the cases indicating that the drug dissolution from all the solid dispersions prepared followed first order kinetics. Dissolution efficiency (DE_{30}) values were calculated as per Khan[6]. The first order dissolution rate constants (K_1) and dissolution efficiency (DE_{30}) values are given in Table 1.

Table 1: Dissolution Parameters of Etoricoxib Solid Dispersions Prepared as per 2^3 Factorial Study

Solid Dispersion Formulation	Composition	Dissolution Rate K_1 (min^{-1})X 10^2		Dissolution Efficiency DE_{30} (%)	
		(x±SD)	Increase in K_1 (no.of folds)	(x±SD)	Increase in DE_{30} (no.of folds)
F_1	Etoricoxib	0.23±0.02	-	3.03±0.15	-
F_a	Etoricoxib: Starch Phosphate (1:2)	6.02±0.02	26.74	55.28±1.03	18.26
F_b	Etoricoxib-PVP (2%)	1.85±0.02	8.04	36.61±0.45	12.09
F_{ab}	Etoricoxib: Starch Phosphate (1:2) -PVP (2%) Etoricoxib-PEG 4000 (2%)	11.51±2.21	51.12	70.59±0.50	23.31
F_c	Etoricoxib: Starch Phosphate (1:2) -PEG 4000 (2%)	2.371±0.32	10.54	46.36±0.62	15.31
F_{ac}	Etoricoxib- PVP (2%) – PEG 4000 (2%)	8.063±0.15	35.81	69.66±0.96	23.06
F_{bc}	Etoricoxib: Starch Phosphate (1:2) -PVP (2%)-PEG 4000(2%)	9.987±0.03	44.32	73.56±0.56	24.29
F_{abc}		45.16±3.46	200.59	88.26±0.12	29.15

Much variations was observed in the dissolution rate (K_1) and DE_{30} values of the solid dispersions prepared as per 2^3 factorial study due to the effects of the factors involved. Dissolution parameters K_1 and DE_{30} were subjected to ANOVA to find out the significance of individual main and combined effects of the three factors involved.

ANOVA of K_1 values indicated that the individual as well as combined effects of the three factors in enhancing the K_1 are highly significant ($P<0.01$). ANOVA of DE_{30} values indicated that the individual effects of all the factors A, B and C were highly significant ($P<0.01$).

Solid dispersion F_1 contains etoricoxib alone without the three factors (starch phosphate, PVP K- 30 and PEG 4000) and hence it is considered as control. All other solid dispersion formulations that contain selected combinations of the three factors gave rapid and higher dissolution when compared to control solid dispersion F1.

Among the individual effects, starch phosphate (factor A) gave highest enhancement in the dissolution rate of etoricoxib (26.7 fold) followed by PEG 4000 (10.54 fold) and PVP (8.04 fold). DE_{30} was also increased from 3.03% for etoricoxib pure drug (F_1) to 55.28, 46.36 and 36.61 % respectively with solid dispersions F_a, F_c and F_b. Addition of PVP and PEG 4000 to the solid dispersions in starch phosphate has further increased the dissolution rate and efficiency of etoricoxib. Solid dispersion formulations F_{ac}, F_{ab} and F_{abc} respectively gave 35.81, 51.12 and 200.59 fold increase in the dissolution rate of etoricoxib when compared to etoricoxib pure drug (control).

CONCLUSION

When the individual main and combined effects of the three factors namely starch phosphate (factor A), PVP K- 30 (factor B) and PEG 4000 (factor C) in enhancing the dissolution rate and dissolution efficiency of etoricoxib were evaluated in a 2^3- factorial study, starch phosphate (F_a) gave highest enhancement in the dissolution rate of etoricoxib (26.7 fold) followed by PEG 4000 (F_c) (10.54 fold) and PVP (F_b) (8.04 fold). DE_{30} was also increased from 3.03% for etoricoxib pure drug (F_1) to 55.28, 46.36 and 36.61 % respectively with solid dispersions F_a, F_c and F_b. Addition of PVP and PEG 4000 to the solid dispersions in starch phosphate has further increased the dissolution rate upto 200.59 fold and dissolution efficiency upto 29.15 fold.

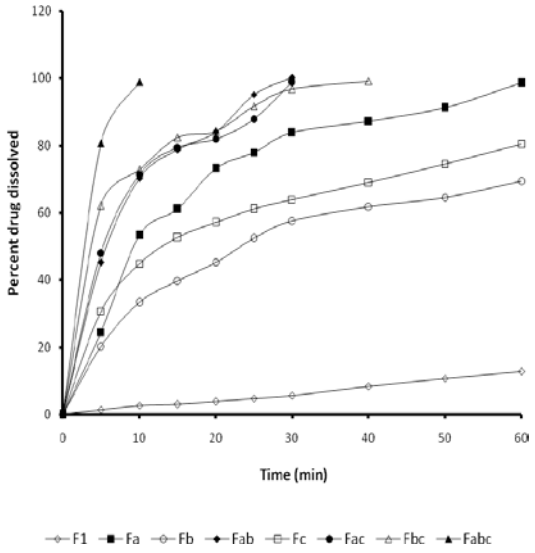

Fig 1: Dissolution Profiles of Etoricoxib Solid Dispersions Prepared as per 2^3 Factorial Study

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